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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/566,057	02/02/2007	Naoyuki Yamamoto	04703/0203798-US0	2082

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DARBY & DARBY P.C.
P.O. BOX 770
Church Street Station
New York, NY 10008-0770

EXAMINER	
KOSAR, AARON J	
ART UNIT	**PAPER NUMBER**
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/566,057	YAMAMOTO ET AL.	
	Examiner	Art Unit	
	Aaron J. Kosar	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/25/06; 11/02/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-4 are pending and have been examined on their merits.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on January 25, 2006 and November 2, 2006, have been considered by the Examiner; however, references which have not been provided in the English language have not been considered beyond the extent of the figures and text appearing/translated into English, to the extent disclosed in the Original Disclosure of the instant Application, or to the extent cited by the Examiner in the present Office action. The IDS have been annotated to indicate the extent considered or lined-through where the reference was wholly not considered.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-4 are rejected under 35 U.S.C. 101, because the claimed invention is directed to non-statutory subject matter. The claims are drawn to a composition which does not require any physical manipulation or isolation or purification. Consequently, the claims may reasonably and broadly be interpreted to include naturally-occurring compositions.

This rejection may be overcome by amending the claims to distinguish the subject matter from that which may be naturally-occurring/product of nature.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 2 recite the limitation "selected from the group.." (and "consisting at least one of.."; however, it is unclear what preceding element is "selected", because there is insufficient antecedent basis for this limitation in the claim. Additionally, it is unclear if the elements of "peptide" (or "enzyme") *or* "a carboxyl terminal", recite the element from which the "selection" is drawn. Thus, it is unclear if the species (e.g. Ile-Pro) are holoproteins or if the species are C-terminal domains which may include other proteins. Since each interpretation is a reasonable interpretation of the claims and each interpretation embraces distinct metes and bounds, one of skill would not be apprised as to what Applicant intends to claim, rendering the claims indefinite; however, this ground of rejection may be overcome by clarifying the antecedent basis in the claims, for example, by reciting "wherein the *in vivo* indigestible peptide is selected.." and "the *in vivo* indigestible peptide consisting of.." in the respective claims.

Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by KARIYA (**CE**:PTO/SB/08 11/02/2006) *or* HELLBERG (**CB**:PTO/SB/08 1/25/2006) *or* KATO (**CC**:PTO/SB/08 11/02/2006) *or* GOMAZKOV (**CC**:PTO/SB/08 1/25/2006) *or* HEINS (**CA**:PTO/SB/08 11/02/2006).

The claims are generally drawn to a peptide composition having a proline C-terminus and species of di- and tripeptide sequences. The dependent claims are further drawn to a composition comprising the peptide composition. The dependent claims are also further drawn to compositions comprising a medicine or food, wherein the medicine or food comprises the peptide-comprising composition (i.e. a medicine/food comprising the angiotensin converting enzyme (ACE) inhibitor).

KARIYA anticipates the claims by teaching a composition comprising the peptides Arg-Pro (wherein Pro is a C-terminal residue). Although Kariya is silent with respect the properties of ACE inhibition or hypotensive effect, Kariya teaches the minimal structural elements of the instant claims. Thus the composition taught by Kariya, reciting identical components as the instant claims, and absent evidence to the criticality of some undisclosed element(s), would be expected to intrinsically possess the claimed properties.

HELLBERG anticipates the claims by teaching the dipeptides Ile-Pro (IP) and Arg-Pro (RP). Hellberg also teaches that these dipeptides are angiotensin converting enzyme (ACE) inhibitors (e.g. table 2, page 419).

KATO anticipates the claims by teaching the species Arg-Pro. Kato also teaches that "X-Pro" is cleaved from structures having the formula $H\text{-}R_1\text{-}R_2\text{-}R_3$, wherein R_1 is an amino acid (X)

with a free amino terminus, including the species Glu and Arg; wherein, R_2 is Pro; and wherein R_3 is the cleavable group comprising *p*-nitroaniline (pNA), amino acids, or peptides.

GOMAZKOV anticipates the claims by teaching the species of dipeptides, Met-Pro (page 279, "методы исследования"(research methods), ¶1).

HEINS anticipates the claims by teaching dipeptides of the formula X_{aa}-Pro wherein X_{aa} is any L-α-amino acid with a free amino group. Heins also teaches reacting X_{aa}-Pro-pNA with dipeptidyl peptidase IV to liberate *p*-nitroaniline (pNA) and the corresponding dipeptides Ile-Pro, Glu-Pro, and Gln-Pro. Thus the composition taught by Heins, reciting identical components as the instant claims, and absent evidence to the criticality of some undisclosed element(s), would be expected to intrinsically possess the claimed properties.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

*This application currently names **joint inventors**. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).*

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over HEINS (**CA**:PTO/SB/08 11/02/2006).

The general teachings of the claims are above.

The general teachings of HEINS are above.

To the extent that Heins is silent in itemizing all of the claimed species of dipeptides, it would have been obvious to make a composition having X_{aa}-Pro structure, because Heins teaches that in the assay (cleavage of an X_{aa}-Pro-pNA with dipeptidylpeptidase IV) that the "X" amino acid residue preceding proline "is any L-α-amino acid with a free amino group"(page 30, right column). Heins also teaches X-Pro-pNA → X-Pro + pNA for 14 of the 20 standard amino acids as the "X" residue (various; table I). Since Heins teaches a *representative number of species* of dipeptides from a *finite number of species*, and because Heinz teaches that the reaction/assay may include any L-α-amino acid, it would have been *prima facie* obvious to make and use any L-α-amino acid-substituted species of the genus of X_{aa}-Pro dipeptides, including the species of the instant claims.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over YAMAMOTO (US 6,994,987 B1) or NAKAMURA (Nakamura, et al. Journal of Dairy Science 1995, 78(4), 777-783) in view of GREENBERG (Greenberg, R., et al "Human β-Casein: Amino Acid Identification of Phosphorylation Sites" The Journal of Biological Chemistry. 1984, 259(8), 5132-5138.) and MARUYAMA (Maruyama, et al JP 02-036127 and JP 10-212245).

The teachings of the claims are above.

YAMAMOTO teaches a composition comprising casein hydrolysates comprising Ile-Pro-Pro (IPP) and Val-Pro-Pro (VPP)(abstract, examples, detailed description (various); claims 1 and 3). Yamamoto teaches the isolated/digested sequences of IPP and VPP (SEQ ID 15 and 27) and sequences comprising the tripeptides (SEQ ID 1-14 and 16-26)(column 3). Yamamoto also teaches the composition comprising IPP and VPP. Yamamoto also teaches that IPP and VPP are hypotensive compositions (abstract).

NAKAMURA teaches that the compositions of IPP and VPP are angiotensin I converting enzyme (ACE) inhibitors.

GREENBERG teaches that casein from bovine casein comprises the sequences including the X-Pro-Pro (XPP) tripeptides: VPP, IPP, *and Leu-Pro-Pro (LPP).*

MARUYAMA teaches that LPP is an inhibitor of angiotensin I converting enzyme. Maruyama also teaches that the tripeptide is useful as "a pharmaceutical product, functional food, etc"(abstract).

To the extent that Yamamoto is silent regarding the Ser-Pro-Pro (SPP) tripeptide, it would have been obvious to make an XPP composition comprising SPP. Yamamoto teaches the representative XPP species, IPP and VPP. Wherein Maruyama teaches that in the source of IPP and VPP of Yamamoto, LPP would be expected to be an intrinsic component of a digest comprising IPP and VPP, it would have been further obvious to supplement/substitute the IPP/VPP/LPP compositions with an XPP composition.

It would have been obvious, because XPP species are known in the art, including the representative species IPP, VPP, and LPP. One would have been motivated to make an XPP, including SPP, because Nakamura and Maruyama teach that XPP compositions including representative species IPP, VPP, and LPP are known in the art; because XPP tripeptides comprise a finite number of species; because the species of XPP tripeptides share a common core structure (C-terminal proline, penultimate proline, N-terminal amino acid); and because the XPP tripeptides are useful for the same purpose as hyptotensives/ antihypertensives/ ACE inhibitors. One would have had a reasonable expectation of success in making an XPP composition because peptide synthesis/enzymatic cleavage is routine in the art and because the representative

tripeptide species IPP/VPP/LPP are considered so close in structure within the finite genus of XPP as to be representative of the genus and thus expected to function similarly to the other proline-terminated tripeptide species.

Thus, in the absence of evidence as to the criticality of the selection of a particular amino acid X or in the absence of evidence to the contrary, the XPP species including SPP would have been *prima facie* obvious for the reasons above. "A prima facie case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991)." *See* MPEP § 2144.09.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

Additionally, while not relied upon in the arguments above, please note, Applicant's disclosure of selecting VPP as the representative *in vivo* XPP species for absorbance studies (Referential Example 1), may be interpreted as further demonstration of the close relatedness of the species of XPP as argued above.

Please note, since the Office does not have the facilities for examining and comparing Applicants' composition with the composition of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. *See In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980), and "as a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith." *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972).

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over KARIYA (**CE**:PTO/SB/08 11/02/2006) *or* HELLBERG (**CB**:PTO/SB/08 1/25/2006) *or* KATO (**CC**:PTO/SB/08 11/02/2006) *or* GOMAZKOV (**CC**:PTO/SB/08 1/25/2006) *or* HEINS (**CA**:PTO/SB/08 11/02/2006) or YAMAMOTO (US 6,994,987 B1)/NAKAMURA (Nakamura, et al. Journal of Dairy Science 1995, 78(4), 777-783) in view of GREENBERG (Greenberg, R., et al "Human β-Casein: Amino Acid Identification of Phosphorylation Sites" The Journal of Biological Chemistry. 1984, 259(8), 5132-5138.)/MARUYAMA (Maruyama, et al JP 02-036127 and JP 10-212245) as argued above and in further view of BASTIN (Bastin, R.J., et al., Organic Process Research and Development, 2000, 4(5), pages 427-435).

The teachings of the instant claims and the prior art of KARIYA, HELLBERG, KATO, GOMAZKOV, HEINS, YAMAMOTO, NAKAMURA, GREENBERG, and MARUYAMA are above.

The difference between the instant claims and the teachings of primary references, is that although the primary references teach the compound/composition having a pharmaceutical activity (hypotensives/antihypertensives/ACE inhibitors), the primary references are silent with respect to teaching the compositions in salt form to the extent as instantly claimed.

Bastin teaches making salt compositions by teaching various pharmaceutically acceptable salt forms, by class and example (Table 1, page 428). Bastin also teaches that, "Although the choice of salt is governed largely by the acidity or basicity of the ionisable group, safety of the counterion, drug indications, route of administration and the intended dosage form must also be considered. Toxicological and pharmacological implications of the selected salt former must be considered as well as the effects of the parent drug. Salt formers can be subdivided into a number of categories depending upon their functionality and purpose. Some of the most frequently used examples are listed in Table 1." (page 428).

Bastin teaches that, "The vast majority of salts are developed to enhance the aqueous solubility of drug substances." (page 428). "Occasionally, salts may be also prepared to decrease drug substance solubility for use in suspension formulations where very low solubility is necessary to prevent 'Ostwald ripening', for taste-masking, or to prepare an extended release product" (page 428).

"Salts are also frequently prepared for the reasons other than solubility modification;.. [such as to] achieve adequate physical stability or for taste masking.., to modify the

pharmacokinetic profile of the drug .. [or] to mill or micronise the active ingredient to achieve adequate homogeneity." (page 429).

It would have been obvious to the artisan at the time of the invention to have made any salt form, including the instantly claimed salt forms, as Bastin teaches salts forms of pharmaceuticals are routinely synthesizes in the endeavor to alter solubility, increase physical stability, alter the pharmacokinetics of the compound, taste-masking, or increase homogeneity of the active substance in a micronised particle formulation.

One would have been motivated to make each salt form, for the reasons set forth above and those disclosed within the reference, including increasing the solubility of the active pharmaceutical.

One would have a reasonable expectation for success in making the pharmaceutical salts, as Bastin teaches salt formation of pharmaceutical compounds is a routine practice of the skilled artisan.

Furthermore, Bastin is relied upon for the reasons discussed above. If not expressly taught by Bastin, based upon the overall beneficial teaching provided by this reference with respect salt selection, optimization, and formation of pharmaceutical salts, in the manner disclosed therein, the adjustments of particular conventional working conditions (e.g., selection and/or optimization of the salt form), is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at

the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

No claims are allowed.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

BOMAN (**CB**:PTO/SB/08, 11/02/2006) *teaches Arg-Pro-pNA to yield the species Arg-Pro and liberated pNA, considered redundant to the teachings above.*

HATA (Hata, Y., et al. A Placebo-Controlled Study of the Effects of Sour Milk on Blood Pressure in Hypertensive Subjects" The American Journal of Clinical Nutrition, U. S, Nov, 1996, 64(5), pages 767-771) *teaches that IPP and VPP are antihypertensives, but considered redundant to the teachings above.*

MARUYAMA (Maruyama, S, et al "Angiotensin I-converting Enzyme Inhibitory Activities of Synthetic Peptide Related to the Tandem Repeated Sequence of Maize Endosperm Protein" Agricul.Biol.Chem. 1989, 53(4), 1077-1081) *teaches synthesis, including 430A peptide synthesizer for the automated synthesis of peptides, including tripeptides and dipeptides. Maruyama in the context of the general recitation of di- and tripeptides, is considered redundant to the teachings above.*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aaron J. Kosar whose telephone number is (571) 270-3054. The examiner can normally be reached on Monday-Thursday, 7:30AM-5:00PM, ALT. Friday,EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Aaron Kosar
Examiner, Art Unit 1651

SANDRA E. SAUCIER
PRIMARY EXAMINER